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Filed : May 2, 2002

### REMARKS

Applicants thank the Examiner for her review of the instant application. Claim 4 has been amended; Claims 1-5 remain present for examination. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed.

#### Rejections Withdrawn

Applicants gratefully acknowledge the withdrawal of the rejections of the pending claims for lack of utility and lack of enablement. However, the PTO has mischaracterized Applicants' statements regarding the nature of the supporting evidence previously submitted to the PTO. In particular, the Office Action states:

Applicant relies on more than 100 references, where expression levels of mRNA, measured by quantitative PCR, were found to have a good correlation to the expressed protein levels. ... While the PTO found several references in which protein expression levels did not correlate with mRNA levels measured by quantitative PCR, the majority of the references which were found, including those cited by Applicant, demonstrated a correlation between mRNA levels measured by quantitative PCR and protein expression levels. Applicant asserts that the expression levels of protein correlate to mRNA (cDNA) levels when the cDNA is measured by quantitative PCR (i.e. rt-PCR). Applicant has provided more than 100 references in support of this position. *Office Action* at 3 (emphasis added, citation omitted).

Applicants have submitted as exhibits numerous references in support of their assertion that, generally speaking, differential mRNA expression levels (e.g., tumor tissue vs. normal tissue) result in similar differential expression levels of the encoded protein. In addition, Applicants have submitted several Information Disclosure Statements listing numerous additional references, including those submitted as exhibits. Applicants have not represented to the PTO that all of the references submitted to the PTO in an IDS support Applicants' assertions.

Applicants have also argued that statements by the authors of Hu *et al.* (J. Proteome Res. 2003; 2(4):405-12), and LaBaer (Nature Biotech. 2003; 21:976-977), regarding the significance of differential mRNA expression detected by mRNA microarrays are not relevant to the data relied on by Applicants. Applicants' data in

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Example 18 of the instant application are based on RT-PCR, which is recognized by those of skill in the art as more sensitive and reliable than mRNA microarrays, and therefore the opinions of Hu and LaBaer regarding the significance of differential mRNA data from microarrays is not relevant to the instant application. Applicants' have not argued that microarray data are not reliable, or that all of the supporting references relied on by the Applicants' used quantitative RT-PCR to measure mRNA levels.

Finally, Applicants note for the record that they do not necessarily agree with the PTO's characterization of the references as set forth in the Office Action. Applicants do agree with the PTO's conclusion that "[b]ased on the totality of evidence of record, one of skill in the art would find it more likely than not that an increase in message as measured by rt-PCR would be predictive of an increase in protein expression levels, absence evidence to the contrary."

#### **Rejection Under 35 U.S.C. §102**

The PTO newly rejects Claims 1-5 under 35 U.S.C. §102(a) as allegedly being anticipated by Barnes (WO 00/18904, published April 6, 2000). According to the PTO, the cited reference teaches murine TANGO 215 that is 91.3% identical to SEQ ID NO:38. The reference also teaches antibodies that bind the polypeptide.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The pending claims recite an isolated antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO:38. The cited reference does not explicitly disclose an antibody which specifically binds to the polypeptide of SEQ ID NO:38, and the Examiner has not established that the cited reference inherently discloses an antibody that satisfies the claims. The M.P.E.P. states that:

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is **necessarily** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing **may** result from a given set of circumstances **is not sufficient**." *M.P.E.P.* §2112 ¶IV (8<sup>th</sup> ed. 2004), quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added).

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Thus, the M.P.E.P. and cited case law makes clear that only if an antibody to the proteins disclosed in the cited references necessarily specifically binds to the polypeptide of SEQ ID NO:38 can it be said to render the claimed subject matter anticipated.

As the Examiner herself has noted in Applicants' related application that claims the polypeptide of SEQ ID NO:38, "The specification does not provide sufficient guidance as to which of the amino acids may be changed while 'claimed antigen specificity' structural or functional activity and specificity is retained. Furthermore, Lederman et al. disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document) and Li et al. disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document)." *Office Action dated December 26, 2006, in Appl. No. 10/063,545* at page 6.

While it might be possible or even probable that an antibody to the protein disclosed in the cited reference, which is only 91.3% identical to the claimed protein, might also specifically bind the polypeptide of SEQ ID NO:38, such an antibody does not necessarily do so since the antibody could bind to one of the locations where there is a difference between the two polypeptides. "Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing may result from a given set of circumstances **is not sufficient**.'" *M.P.E.P.* §2112 ¶IV (8<sup>th</sup> ed. 2004), quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added).

The cited reference does not explicitly disclose the claimed antibody, and even if it is possible or probable that an antibody to the proteins disclosed in the references satisfies the claim limitations, it does not necessarily do so. Therefore the limitation "specifically binds to the polypeptide of SEQ ID NO:38" is neither explicitly nor inherently described in the cited art. In the absence of an express or inherent disclosure of the claimed subject matter, the cited reference does not anticipate the rejected claims.

Further, Applicants have shown possession of as much of the claimed invention as allegedly disclosed in the cited reference prior to its publication. The sequence of SEQ ID NO:38 was first disclosed in U.S. Provisional Application 60/096959, filed August 18, 1998. The invention as presently claimed was clearly possessed by Applicants at least by the filing date of the provisional application, as a reading of the entire provisional application makes clear. For

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example, the provisional application discloses antibody that binds the claimed polypeptide, as well as humanized antibodies and monoclonal antibodies. The provisional application also discloses the manufacture of antibodies to SEQ ID NO:38, and their use to detect expression of the polypeptide in specific tissue types. Thus, the provisional application clearly demonstrates possession of the invention by Applicants by at least its August 18, 1998 filing date, which is prior to the effective date of the cited reference, April 6, 2000.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 U.S.P.Q. 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention."

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is

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not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need **not** demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where there is a disclosure that predates the cited reference. The PTO asserts that the cited reference discloses a sequence which is 93.1% identical to SEQ ID NO:38 and antibodies thereto. Applicants demonstrated, by means of the disclosure of SEQ ID NO:38 and antibodies thereto in their provisional application filed August 18, 1998, that they were in possession of so much of the claimed invention as disclosed in the cited reference prior to its publication. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and respectfully request that the PTO reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 102(a).

**Rejection Under 35 U.S.C. §112, second paragraph**

Claim 4 has been rejected as being indefinite. The claim has been amended as suggested by the Examiner to obviate the rejection.

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### CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 22, 2007

By: AnneMarie Kaiser  
AnneMarie Kaiser  
Registration No. 37,649  
Attorney of Record  
Customer No. 30,313  
(619) 235-8550

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